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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/512,739	10/27/2004	Eric G. Marcusson	ISPH-0862	2119

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/512,739	MARCUSSON ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *October 27, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are pending in the instant application.

Claims 1-16 have been examined on the merits.

Information Disclosure Statement

Applicant's information disclosure statement filed October 27, 2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

Priority

Applicant's reference to priority in the first sentence of the specification is acknowledged. It is noted that the instant application is the national stage entry of PCT/US03/18320, filed on June 10, 2003, which claims priority from Provisional Application 60388074, filed June 11, 2002.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-16 provides for the use of an inhibitor of interleukin 12 p35 in the manufacture of a medicament to inhibit the differentiation of adipocyte cells, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14-16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 14 and 26 of U.S. Patent No. 6,399,379 ('379), in view of Moller et al. (Immunology, 1997 Vol. 91:197-203), and Windmeier et al. (Biochemical Pharmacology, 1996 Vol. 51, pages 577-584, made of record in Applicant's Information Disclosure Statement filed October 27, 2004, see reference BC).

Claim 1 is drawn to a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation is inhibited. It is noted that the instant specification does not define the term, "adipocyte cell". In the absence of such a definition, the Examiner has interpreted the term, "adipocyte cell" to be simply "a fat cell" as defined in

Merriam-Webster's Collegiate Dictionary, Tenth Edition, (1996) (see attached definition). It is also noted that the instant specification does not define the term, "preadipocyte cell". Applicant is reminded that that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Given its broadest reasonable interpretation, the Examiner has interpreted the term, "preadipocyte cell" to simply be a fat cell as well, considering the broad definition of the term "adipocyte cell" as described by Merriam-Webster's Collegiate Dictionary.

'379 teaches and claims a method of inhibiting the expression of Interleukin 12 p35 in cells or tissues *in vitro* comprising administering an antisense oligonucleotide targeted to a nucleic acid molecule encoding Interleukin 12 p35 (see claims 14 and 26).

'379 does not teach method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35.

Moller et al. teach the inhibition of Interleukin 12 p35 expression by pentoxifylline (see Abstract and Figure 4). It is noted that Moller et al. is being relied upon to teach that pentoxifylline is an inhibitor of Interleukin 12 p35 mRNA expression.

Windmeier et al. teach the effects of pentoxifylline on the function of cultured rat liver fat-storing cells (see Abstract). Specifically, Windmeier et al. teach that pentoxifylline inhibits the transdifferentiation of fat-storing cells to myofibroblasts (see Figure 1 and page 580, first column).

The prior art teaches a relationship between inhibiting the differentiation of adipocyte cells by administering an inhibitor of Interleukin 12 p35 (see Windmeier et al.).

It would have been obvious to one of ordinary skill in the art at the time of filing to devise a method of inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35 using the teachings of '379 and following the methods and motivation of Moller et al. and Windmeier et al.

It would have been *prima facie* obvious to devise a method for inhibiting the expression of Interleukin 12 p35 in adipose cells since Moller et al. taught pentoxifylline is a specific inhibitor of Interleukin 12 p35 and since Windmeier et al. taught pentoxifylline modulates the differentiation of adipose cells. '379 teaches an antisense inhibitor of Interleukin 12 p35. It would have been obvious to one of ordinary skill in the art to use an antisense inhibitor of Interleukin 12 p35 in the method taught by Windmeier et al. since and it is obvious in the art to substitute one functional equivalent for another, particularly when they are to be used for the same purpose. See MPEP 2144.06.

One of ordinary skill in the art would have been motivated to devise a method for inhibiting the expression of Interleukin 12 p35 in adipose cells, wherein adipocyte differentiation is inhibited since Windmeier et al. taught an inhibitor of Interleukin 12 p35 modulates (e.g. inhibits) the differentiation of adipose cells which is important in weight maintenance and obesity.

One of ordinary skill in the art would have expected success at devising a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35 since '379 explicitly teaches the

successful inhibition of Interleukin 12 p35 in cells and Windmeier et al. taught the successful use of an Interleukin 12 p35 inhibitor in adipose specific cells.

Therefore, the instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation is inhibited. Claims 2-4 are drawn to a method for inhibiting lipid accumulation in a cell comprising contacting a cell with an inhibitor of Interleukin 12 p35, whereby lipid accumulation in the cell is inhibited. Claims 5-16 are drawn to methods of treating a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a

mammal, comprising administering an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation, lipid accumulation, or triglyceride accumulation is inhibited.

The specification provides one example of an inhibitor of Interleukin12 p35, ISIS 138969, represented by SEQ ID NO:1, which is an antisense oligonucleotide targeted to a nucleic acid molecule encoding Interleukin 12 p35. It is noted that the instant specification at page 23, lines 21-23 discloses that other antisense inhibitors of Interleukin 12 p35, are disclosed in U.S. Patent No. 6,399,379 (U.S. Patent No. 6,399,379 being made of record in Applicant's Information Disclosure Statement filed October 27, 2004, see reference AA). Now then, referring to U.S. Patent No. 6,399,379, it is noted that the patent teaches dozens of antisense oligonucleotide inhibitors of Interleukin 12 p35, which are targeted to a nucleic acid molecule encoding human Interleukin 12 p35. It is noted that SEQ ID NO:23 of U.S. Patent No. 6,399,379 is the same antisense oligonucleotide as SEQ ID NO:1 of the instant application. The prior art also teaches antibodies to human interleukin 12 which have been demonstrated to neutralize the biological activity of interleukin 12 (see Carter et al., Hybridoma, 1997 Vol. 16, pages 363-369). The prior art also teaches a human IL-12 antagonist, wherein said antagonist is an antibody immunoreactive with IL-12, and wherein said antibody is specific for IL-12 p35 (see U.S. Patent No. 6,706,264).

At the outset, it is noted that the rejected claims do not recite any sequence identifier relating to Interleukin 12 p35. This sequence is thus considered to be defined by its function (i.e. the activity of Interleukin 12 p35) rather than by any one specific structure. Accordingly, the claims encompass inhibitors of Interleukin 12 p35, or any

such molecule with analogous Interleukin 12 p35 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Interleukin 12 p35 activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written

description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to synthesize the inhibitors of Interleukin 12 p35 and use them in the methods as claimed, one of skill would first need the sequence of the Interleukin 12 p35. Although the instant specification teaches a single antisense oligonucleotide inhibitor of human Interleukin 12 p35, and the prior art teaches antibody inhibitors of human interleukin 12, the claims embrace inhibitors of Interleukin 12 p35 directed to *any* sequence of *any* Interleukin 12 p35, or any such molecule with analogous Interleukin 12

p35 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Interleukin 12 p35 activity. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the claimed inhibitors encompassed by the instant invention, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of inhibitors of Interleukin 12 p35 is considered to include not only the Interleukin 12 p35 sequence taught in the instant invention and the prior art, but also any such molecule with analogous Interleukin 12 p35 activity, known or yet to be discovered. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision any inhibitors of Interleukin 12 p35, other than those described in the instant specification and the prior art, one of skill would not be convinced that applicants were in possession of any inhibitors of Interleukin 12 p35 sequences that are heretofore undescribed.

******

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal, comprising administering an inhibitor of Interleukin 12

p35, wherein the inhibitor is pentoxifylline or an antibody immunoreactive with IL-12, whereby adipocyte differentiation, lipid accumulation, or triglyceride accumulation is inhibited, or a method of inhibiting the differentiation of an adipocyte cell *in vitro* or inhibiting lipid accumulation in a cell *in vitro*, comprising administering an antisense oligonucleotide targeted to a nucleic acid encoding human Interleukin 12 p35, wherein said antisense inhibits human Interleukin 12 p35, does not reasonably provide enablement for a method of treating a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal comprising administering *any* inhibitor of Interleukin 12 p35, or a method of inhibiting the differentiation of an adipocyte cell *in vivo* or inhibiting lipid accumulation in a cell *in vivo*, comprising administering an antisense oligonucleotide, which inhibits Interleukin 12 p35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

Claim 1 is drawn to a method for inhibiting the differentiation of an adipocyte cell comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation is inhibited. Claims 2-4 are drawn to a method for inhibiting lipid accumulation in a cell comprising contacting a cell with an inhibitor of Interleukin 12 p35, whereby lipid accumulation in the cell is inhibited. Claims 5-16 are drawn to methods of treating a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a

mammal, comprising administering an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation, lipid accumulation, or triglyceride accumulation is inhibited. It is noted that the instant specification at page 11, last paragraph discloses, "Any inhibitor of interleukin 12 p35 may be employed in accordance with the present invention". The instant specification at page 12, lines 7-11 further discloses, "Inhibitors of Interleukin 12 p35 include small molecules, preferably organic small molecule compounds; antibodies; peptides and peptide fragments, particularly Interleukin 12 p35 dominant negative peptides and fragments, and the like".

At the outset, it is noted that the instant specification is heavy on methods of using antisense oligonucleotide inhibitors of Interleukin12 p35. In fact, the instant specification provides only one working example of a method of using an inhibitor of Interleukin12 p35, namely ISIS 138969, represented by SEQ ID NO:1, which is an antisense oligonucleotide targeted to a nucleic acid molecule encoding human Interleukin 12 p35. For example, the specification teaches a method of lowering triglyceride accumulation in cultured preadipocytes following treatment with an antisense inhibitor of Interleukin 12 p35, ISIS 138969 (see Example 1). The specification also teaches that differentiation of cultured preadipocytes to adipocytes was inhibited by treatment with interleukin 12 p35 antisense inhibitor, ISIS 138969 (see Example 3).

The prior art teaches pentoxifylline, a non-specific phosphodiesterase inhibitor, is an inhibitor of Interleukin 12 p35 (IL-12 p35) mRNA expression (see Moller et al. (Immunology, 1997 Vol. 91, pages 198-203, at Abstract and Figure 4). The prior art

further teaches that pentoxifylline inhibits the transdifferentiation of fat-storing cells to myofibroblasts (see Windmeier et al. (Biochemical Pharmacology, 1996 Vol. 51, pages 577-584, made of record in Applicant's Information Disclosure Statement filed October 27, 2004, see reference BC). The prior art further teaches the effect of pentoxifylline on blood glucose control in type I and II diabetics has an important and promising clinical impact and pentoxifylline offers a promising mode of treatment (see Raptis et al., Acta Diabetol Lat., 1987 Vol. 24:181-192). The prior art also teaches methods of treating autoimmune conditions, including diabetes, comprising administering to a human an IL-12 antagonist, wherein said antagonist is an antibody immunoreactive with IL-12, and wherein said antibody is specific for IL-12 p35 (see U.S. Patent No. 6,706,264). It is noted that the instant specification is fully enabled for what is taught in the prior art.

However, the prior art also teaches that inhibition of interleukin 12 p35 has adverse effects on the differentiation of adipocyte cells. For example, the prior art teaches 1,25-Dihydroxyvitamin D_3, a sterol hormone, is an inhibitor of IL-12 p35 mRNA expression (see D-Ambrosio et al. Journal of Clinical Investigation, 1998 Vol. 101:252-262, at Abstract and Figure 2). Vu et al. (Endocrinology, 1996 Vol. 137:1540-1544) teaches 1,25-Dihydroxyvitamin D_3 modulates (e.g. induces) the differentiation of adipocyte cells. Specifically, Vu et al. teach 1,25-Dihydroxyvitamin D_3 induces, not inhibits, the differentiation of 3T3-L1 preadipocyte cells to mature, terminally differentiated adipocyte cells (see page 1544, last paragraph and Figure 5).

Neither the specification as filed, nor the prior art provide sufficient guidance or appropriate examples that would enable a skilled artisan to practice the disclosed

methods using other inhibitors of Interleukin 12 p35, other than antisense oligonucleotides, pentoxifylline or an antibody immunoreactive with IL-12. Additionally, a person skilled in the art would recognize that neither the specification as filed, nor the prior art provide sufficient guidance or appropriate examples that would enable a skilled artisan to practice the disclosed methods of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell *in vivo*, or methods of treatment, comprising administering an antisense oligonucleotide which inhibits Interleukin 12 p35, based solely on its performance *in vitro*. Thus, although the specification contemplates and claims methodologies of using *any* inhibitor of Interleukin 12 p35 in a method of treating an animal having a disease or condition associated with adipocyte differentiation, whereby adipocyte differentiation is inhibited, such a disclosure would not be considered enabling since the prior art has shown that some inhibitors of Interleukin 12 p35 actually induce adipocyte differentiation (see Vu et al.). Further, although the specification contemplates and claims methods of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell *in vivo*, or methods of treatment, comprising administering an antisense oligonucleotide inhibitor of Interleukin 12 p35, such a disclosure would not be considered enabling since the prior art has shown that the state of antisense-mediated gene therapy is highly unpredictable.

The factors listed below have been considered in the analysis of enablement regarding antisense therapy:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;

(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligonucleotides in treating disease: "gene inhibition by antisense oligonucleotides has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, paragraphs 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligonucleotides by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism".

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (see page 4503, paragraphs 1

and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligonucleotides as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligonucleotide depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligonucleotide to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their

target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Branch et al. discuss the problems pertaining to non-specific oligonucleotide interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, these effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit" (Page 46, second column).

Tamm et al. concludes by stating that, "until the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Thus, it is maintained that the prior art at the time of Applicants' filing would not enable the use of any/all inhibitors of Interleukin 12 p35 for the treatment of diseases or conditions associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal. This is particularly in view of the fact that Vu et al. disclose that some inhibitors of Interleukin 12 p35 actually induce adipocyte differentiation. It is also maintained that the prior art at the time of Applicant's filing would not enable the *in vitro* use of antisense oligonucleotides to support claims directed to the *in vivo* use of antisense, let alone claims directed to therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of the lowering of triglyceride accumulation or the inhibition of differentiation in cultured preadipocytes following treatment with an antisense inhibitor of Interleukin 12 p35 enough to overcome the unpredictability and challenges of the treatment of any/all diseases or conditions associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal, as exemplified in the references above. Thus, the specification as filed fails to provide any particular guidance which resolves the known

unpredictability in the art associated with appropriate *in vivo* delivery and therapeutic use of the antisense administered, and specifically regarding the methods claimed.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of those inhibitors of Interleukin 12 p35, including antisense oligonucleotides, that are successfully delivered to target sites in appropriate cells and/or tissues such that treatment of diseases or conditions associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal is achieved. Particularly, since the specification fails to provide any real guidance for the methods of using antisense *in vivo*, and since resolution of the various complications in regards to targeting a particular gene in an organism is unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Windmeier et al. (Biochemical Pharmacology, 1996 Vol. 51, pages 577-584, made of record in Applicant's Information Disclosure Statement filed October 27, 2004, see reference BC), as evidenced by Moller et al. (Immunology, 1997 Vol. 91, pages 198-203).

Claim 1 is drawn to a method for inhibiting the differentiation of an adipocyte cell *in vitro*, comprising contacting a preadipocyte cell with an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation is inhibited. Claims 2-4 are drawn to a method for inhibiting lipid accumulation in a cell *in vitro*, comprising contacting a cell with an inhibitor of Interleukin 12 p35, whereby lipid accumulation in the cell is inhibited. It is noted that the instant specification does not define the term, "adipocyte cell". In the absence of such a definition, the Examiner has interpreted the term, "adipocyte cell" to be simply "a fat cell" as defined in Merriam-Webster's Collegiate Dictionary, Tenth Edition, (1996) (see attached definition). It is also noted that the instant specification does not define the term, "preadipocyte cell". Applicant is reminded that that during patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See MPEP § 2111-2116.01. Given its broadest reasonable interpretation, the Examiner has interpreted the term, "preadipocyte cell" to

simply be a fat cell as well, considering the broad definition of the term "adipocyte cell" as described by Merriam-Webster's Collegiate Dictionary.

Windmeier et al. disclose the effects of pentoxifylline on the function of cultured rat liver fat-storing cells (see Abstract). Specifically, Windemier et al. disclose that pentoxifylline inhibits the transdifferentiation of fat-storing cells to myofibroblasts (see Figure 1 and page 580, first column).

It is noted that Moller et al. is being relied upon as evidence to teach that pentoxifylline is an inhibitor of Interleukin 12 p35 mRNA expression (see Abstract and Figure 4).

The burden of establishing whether the prior art method has the function of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell, including an adipocyte, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant

to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the method of administering pentoxifylline to cultured fat-storing cells disclosed by Windmeier et al. would or would not have the additional function of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell as claimed. Therefore, absent evidence to the contrary, claims 1-4 are anticipated by Windmeier et al.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cigolini et al. (Atherosclerosis, 1999 Vol. 143:81-90, made of record in Applicant's Information Disclosure Statement filed October 27, 2004, see reference BB), as evidenced by Moller et al. (Immunology, 1997 Vol. 91, pages 198-203).

The claims are as described above in the 35 U.S.C. 102(b) rejection as being anticipated by Windmeier et al. as evidenced by Moller et al.

Cigolini et al. disclose cultured human adipose tissues incubated with pentoxifylline (see Abstract). Specifically, Cigolini et al. disclose human fat biopsies of subcutaneous adipose tissue were incubated in culture medium with pentoxifylline and Northern blots of PAI-1 mRNA in human adipose tissue was measured (see Figure 9).

It is noted that Moller et al. is being relied upon as evidence to teach that pentoxifylline is an inhibitor of Interleukin 12 p35 mRNA expression (see Abstract and Figure 4).

The burden of establishing whether the prior art method has the function of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell, including an adipocyte, under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the method of administering pentoxifylline to human fat biopsies of subcutaneous adipose tissue disclosed by Cigolini et al. would or would not have the additional function of inhibiting the differentiation of an adipocyte cell or inhibiting lipid accumulation in a cell as claimed. Therefore, absent evidence to the contrary, claims 1-4 are anticipated by Cigolini et al.

Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Raptis et al. (Acta Diabetol Lat., 1987 Vol. 24:181-192) as evidenced by Moller et al. (Immunology, 1997 Vol. 91, pages 198-203).

Claims 1-4 are as described above in the 35 U.S.C. 102(b) rejection as being anticipated by Windmeier et al. as evidenced by Moller et al. Claims 5-16 are drawn to methods of treating a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels in a mammal comprising administering an inhibitor of Interleukin 12 p35, whereby adipocyte differentiation, lipid accumulation, or triglyceride accumulation is inhibited. It is noted that the instant specification discloses and claims that a disease or condition associated with adipocyte differentiation, excess adipocytes, lipid accumulation, or high glyceride levels is diabetes (see, for example, claims 5-10, 12, and 13).

Raptis et al. disclose the oral administration of pentoxifylline to patients with Type I and Type II diabetes (see page 181). Specifically, Raptis et al. disclose that pentoxifylline administration in diabetic patients led to a decrease of absolute blood glucose values (see page 185, last paragraph and Figures 2 and 3). Raptis et al. postulate that, "Pentoxifylline ameliorates the disturbed carbohydrate metabolism in diabetics" (see page 188, first full paragraph) and "Pentoxifylline exerts a favorable influence on carbohydrate metabolism in diabetics" (see page 188, last paragraph). Raptis et al. also disclose, "It can be said that the demonstrated effect of pentoxifylline on 24-h blood glucose control in type I and II diabetics has an important and promising

clinical impact" and "Pentoxifylline... offers a promising mode of treatment" (see page 189, last paragraph).

It is noted that Moller et al. is being relied upon as evidence to teach that pentoxifylline is an inhibitor of Interleukin 12 p35 mRNA expression (see Abstract and Figure 4).

The burden of establishing whether the prior art method has the function of inhibiting adipocyte differentiation, lipid accumulation, or triglyceride accumulation in a mammal under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the method of

administering pentoxifylline to human patients with diabetes disclosed by Raptis et al. would or would not have the additional function of inhibiting adipocyte differentiation, lipid accumulation, or triglyceride accumulation in a mammal as claimed. Therefore, absent evidence to the contrary, claims 1-16 are anticipated by Raptis et al.

Claims 1-16 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,706,264 ('264).

The claims are as described above in the 35 U.S.C. 102(b) rejection as being anticipated by Raptis et al. as evidenced by Moller et al.

'264 discloses and claims methods of treating autoimmune conditions comprising administering to a human an IL-12 antagonist, wherein said antagonist is an antibody immunoreactive with IL-12 (see Abstract and claim 1). It is noted that the autoimmune condition disclosed by '264 is diabetes (see Abstract, column 2, lines 32-42, and claims 1, 6, and 7) and the antagonistic IL-12 antibody is an IL-12, p35 specific antagonist (see columns 3 and 4, lines 65-66 and 39-62, respectively).

The burden of establishing whether the prior art method has the function of inhibiting adipocyte differentiation, lipid accumulation, or triglyceride accumulation in a mammal under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977).

"When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the method of administering pentoxifylline to human patients with diabetes disclosed by '264 would or would not have the additional function of inhibiting adipocyte differentiation, lipid accumulation, or triglyceride accumulation in a mammal as claimed. Therefore, absent evidence to the contrary, claims 1-16 are anticipated by '264.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
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